

EXHIBIT A



(12) **United States Patent**
Palepu et al.

(10) **Patent No.:** **US 12,138,248 B2**
(45) **Date of Patent:** ***Nov. 12, 2024**

(54) **FORMULATIONS OF BENDAMUSTINE**

(71) Applicant: **Eagle Pharmaceuticals, Inc.**, Woodcliff Lake, NJ (US)

(72) Inventors: **Nagesh R. Palepu**, Southampton, PA (US); **Philip Christopher Buxton**, Uxbridge (GB)

(73) Assignee: **Eagle Pharmaceuticals, Inc.**, Woodcliff Lake, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/646,171**

(22) Filed: **Apr. 25, 2024**

(65) **Prior Publication Data**

US 2024/0293372 A1 Sep. 5, 2024

Related U.S. Application Data

(63) Continuation of application No. 18/498,259, filed on Oct. 31, 2023, which is a continuation of application No. 17/412,623, filed on Aug. 26, 2021, now abandoned, which is a continuation of application No. 16/509,920, filed on Jul. 12, 2019, now Pat. No. 11,103,483, which is a continuation of application No. 16/015,656, filed on Jun. 22, 2018, now abandoned, which is a continuation of application No. 15/432,335, filed on Feb. 14, 2017, now Pat. No. 10,010,533, which is a continuation of application No. 15/013,436, filed on Feb. 2, 2016, now Pat. No. 9,572,797, which is a continuation of application No. 14/031,879, filed on Sep. 19, 2013, now Pat. No. 9,265,831, which is a continuation of application No. 13/016,473, filed on Jan. 28, 2011, now Pat. No. 8,609,707.

(60) Provisional application No. 61/299,100, filed on Jan. 28, 2010.

(51) **Int. Cl.**

A61K 9/08 (2006.01)
A61K 31/41 (2006.01)
A61K 31/4184 (2006.01)
A61K 47/10 (2017.01)
A61K 47/12 (2006.01)
A61K 47/18 (2017.01)
A61K 47/20 (2006.01)
A61K 47/22 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 31/4184** (2013.01); **A61K 9/08** (2013.01); **A61K 47/10** (2013.01); **A61K 47/12** (2013.01); **A61K 47/18** (2013.01); **A61K 47/20** (2013.01); **A61K 47/22** (2013.01); **A61K 9/0019** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 31/4184**; **A61K 9/08**; **A61K 47/10**; **A61K 47/12**; **A61K 47/18**; **A61K 47/20**; **A61K 47/22**; **A61K 9/0019**

See application file for complete search history.

(56)

References Cited

U.S. PATENT DOCUMENTS

4,071,620 A	1/1978	Sklar	
4,711,906 A	12/1987	Von et al.	
4,879,286 A	11/1989	Alam et al.	
5,204,335 A	4/1993	Sauerbier et al.	
5,223,515 A	6/1993	Mikura et al.	
5,741,523 A	4/1998	Teagarden et al.	
6,686,365 B2 *	2/2004	Riebesehl A61K 45/06 514/262.1
7,252,799 B2	8/2007	Miekka et al.	
7,772,274 B1	8/2010	Palepu	
8,076,366 B2	12/2011	Courvoisier et al.	
8,344,006 B2	1/2013	Drager et al.	
8,389,558 B2	3/2013	Alakhov et al.	
8,609,707 B2	12/2013	Palepu et al.	
8,791,270 B2	7/2014	Brittain et al.	
9,000,021 B2	4/2015	Sundaram et al.	
9,034,908 B2	5/2015	Sundaram	
9,144,568 B1	9/2015	Sundaram	
9,265,831 B2	2/2016	Palepu et al.	

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2787568 A1	8/2011
CA	2867295 A1	9/2013

(Continued)

OTHER PUBLICATIONS

Scifinder, Hydrolytic degradation of IMET 3393, American Chemical Society, 2018.

(Continued)

Primary Examiner — Ernst V Arnold

(74) *Attorney, Agent, or Firm* — BakerHostetler

(57)

ABSTRACT

Long term storage stable bendamustine-containing compositions are disclosed. The compositions can include bendamustine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable fluid which can include in some embodiments PEG, PG or mixtures thereof and an antioxidant or chloride ion source. The bendamustine-containing compositions have less than about 5% total impurities, on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

22 Claims, No Drawings

US 12,138,248 B2

Page 2

(56) **References Cited**
U.S. PATENT DOCUMENTS

9,572,796 B2 2/2017 Palepu et al.
 9,572,797 B2 2/2017 Palepu et al.
 9,572,887 B2 2/2017 Sundaram
 9,572,888 B2 2/2017 Sundaram
 9,579,384 B2 2/2017 Sundaram et al.
 9,597,397 B2 3/2017 Sundaram
 9,597,398 B2 3/2017 Sundaram
 9,597,399 B2 3/2017 Sundaram
 10,010,533 B2 7/2018 Palepu et al.
 10,052,385 B2 8/2018 Sundaram
 11,103,483 B2 8/2021 Palepu et al.
 11,707,450 B1 7/2023 Chinnari et al.
 2002/0102215 A1 8/2002 Klaveness et al.
 2002/0122768 A1 9/2002 Liu et al.
 2004/0014964 A1 1/2004 Cheesman et al.
 2004/0043069 A1 3/2004 Vanderbilt et al.
 2004/0167152 A1 8/2004 Rubino et al.
 2005/0025702 A1 2/2005 Decicco et al.
 2005/0042285 A1 2/2005 Ukai et al.
 2006/0001597 A1 1/2006 Han
 2006/0035945 A1 2/2006 Attardo et al.
 2006/0128777 A1 6/2006 Bendall et al.
 2006/0159713 A1 7/2006 Brittain et al.
 2006/0205694 A1 9/2006 Alonso et al.
 2007/0116729 A1 5/2007 Palepu
 2008/0118544 A1 5/2008 Wang
 2009/0082416 A1 3/2009 Czarnik
 2009/0209606 A1 8/2009 Bendall et al.
 2009/0264488 A1 10/2009 Cooper et al.
 2009/0325978 A1 12/2009 Onai et al.
 2010/0092474 A1 4/2010 Gallagher et al.
 2010/0145266 A1 6/2010 Orlowski
 2010/0216858 A1 8/2010 Popek et al.
 2010/0247669 A1 9/2010 Eliasof et al.
 2010/0273730 A1 10/2010 Hsu et al.
 2011/0015245 A1 1/2011 Alakhov et al.
 2011/0190363 A1 8/2011 Drager et al.
 2012/0059000 A1 3/2012 Ren et al.
 2012/0071532 A1 3/2012 Cooper et al.
 2012/0157505 A1 6/2012 Labell et al.
 2012/0308516 A1 12/2012 Hlavinka et al.
 2013/0041003 A1 2/2013 Brittain et al.
 2013/0041004 A1 2/2013 Drager et al.
 2013/0177572 A1 7/2013 Chen et al.
 2013/0210878 A1 8/2013 Soppimath et al.
 2013/0210879 A1 8/2013 Palepu et al.
 2013/0217888 A1 8/2013 Shrawat et al.
 2013/0288274 A1 10/2013 Walker et al.
 2014/0094496 A1 4/2014 Sundaram
 2014/0275196 A1 9/2014 Sundaram
 2015/0080444 A1 3/2015 Sundaram et al.
 2018/0185488 A1 7/2018 Sundaram
 2018/0296535 A1 10/2018 Palepu et al.
 2018/0296536 A1 10/2018 Palepu et al.
 2018/0369383 A1 12/2018 Sundaram
 2019/0192659 A1 6/2019 Sundaram
 2021/0393594 A1 12/2021 Palepu et al.
 2023/0115164 A1 4/2023 Palepu et al.
 2023/0115693 A1 4/2023 Palepu et al.

FOREIGN PATENT DOCUMENTS

CA 2867343 A1 9/2013
 CN 1850048 A 10/2006
 CN 101584668 A 11/2009
 CN 102164579 A 8/2011
 CN 104302291 A 1/2015
 DE 80967 A 1/1970
 DE 152989 A1 12/1981
 DE 159289 A1 3/1983
 EP 2326306 A1 6/2011
 EP 2528602 A1 12/2012
 EP 2827862 A1 1/2015
 EP 2827863 A1 1/2015
 JP 2015-160351 A 9/2015

WO 95/19759 A1 7/1995
 WO 99/01118 A2 1/1999
 WO 2001/097860 12/2001
 WO 2001/097861 12/2001
 WO 2001/098294 12/2001
 WO 02/02125 A1 1/2002
 WO 2006/054315 A1 5/2006
 WO 2006/110551 A2 10/2006
 WO 2010/036702 A1 4/2010
 WO 2010/126676 A1 11/2010
 WO 2010/148288 A2 12/2010
 WO 2011/094565 A1 8/2011
 WO 2011/103150 A2 8/2011
 WO 2012/015810 A2 2/2012
 WO 2013/142358 A1 9/2013

OTHER PUBLICATIONS

Seager et al., "Structure of Products Prepared by Freeze-Drying Solutions Containing Organic Solvents", PDA Journal of Pharmaceutical Science and Technology, 1985, vol. 39, No. 4, pp. 161-179.
 Search History issued in connection with PCT/US2013/32295 dated May 10, 2013.
 Search History: Limited Classification Search dated May 10, 2013, PCT/US2013/032295.
 Seedher et al., "Solubilization of Nimesulide—Use of Co-solvents", Indian J. Pharm. Sci., 2003, vol. 65, No. 1, pp. 58-61.
 Shah et al., "Physical, Chemical, and Bioavailability Studies of Parenteral Diazepam Formulations Containing Propylene Glycol and Polyethylene Glycol 400", Drug Development and Industrial Pharm., 2008, vol. 17, No. 12, pp. 1635-1654.
 Shah et al., Physical, Chemical, and Bioavailability Studies of Parenteral Diazepam Formulations Containing Propylene Glycol and Polyethylene Glycol 400, Drug Development and Industrial Pharm., 17:12, 1635-1654 (Oct. 20, 2008).
 Sheskey, Handbook of Pharmaceutical Excipients, 7th Edition, Propyl Gallate, 2012.
 Sigma-Aldrich, Webpage Catalog for poly(ethylene glycol), <http://www.sigmaaldrich.com/catalog/product/aldrich/202398?lang=en&ion- = US#>, accessed Nov. 15, 2015, pp. 1-2.
 Sikora, "Cancer drug development in the post-genomic age", Current Science, 2001, vol. 81 No. 5 pp. 549-554.
 Spectra Analysis, Inc., "Oxidative Degradation of Polyethyleneglycol (PEG) studied by LC-IR", Application Note 016, Mar. 2008.
 Spiegel et al. ("Spiegel", J. Pharma. Sci., 1963, 52(10), 917-927).
 Spiegel et al., "Use of Nonaqueous Solvents in Parenteral Products," Journal of Pharmaceutical Sciences, 1963, vol. 52, No. 10 pp. 917-927.
 Spiegel, et al., "Use of Nonaqueous Solvents in Parenteral Products," J. Pharmac. Sciences, vol. 52, No. 10, pp. 917-927 (1963).
 Strickley, "Solubilizing Excipients in Oral and Injectable Formulations", Pharmaceutical Research 2004, vol. 21, No. 2, pp. 201-230.
 Supplemental European Search Report issued in connection with PCT/US2011/022958 dated Dec. 16, 2013.
 Supplementary European Search Report in related EP 2528602 dated Jan. 2014.
 Tajeja, "Bendamustine: Safety and Efficacy in the Management of Indolent Non-Hodgkin's Lymphoma", Clinical Medicine Insights: Oncology, 2011, vol. 5, pp. 145-156.
 Tajeja, Bendamustine: Safety and Efficacy in the Management of Indolent Non-Hodgkins Lymphoma, Clinical Medicine Insights: Oncology 2011:5 145-156.
 Teagarden et al., "Practical Aspects of Freeze-Drying of Pharmaceutical and Biological Products Using Non-Aqueous Co-Solvent Systems", Chapter 8 in Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products, 2004, pp. 239-276.
 Teagarden et al., "Practical Aspects of Lyophilization Using Non-Aqueous Co-Solvent Systems", Eur. J. Pharma. Sciences, 2002, vol. 15, pp. 115-133.
 Teva Pharmaceuticals International GMBH, et al. v. Apotex Inc., et al—Civil Action 1:17-cv-01164: Defendants Apotex Inc. and Apotex Corp.'s Answer to Complaint, Defenses and Counterclaims (Document 17), dated Nov. 27, 17.

US 12,138,248 B2

Page 3

(56)

References Cited

OTHER PUBLICATIONS

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi USA, LLC.—Civil Action No. 1:17-cv-01201: Answer to Complaint, Separate Defenses, and Counterclaims (Document 10), dated Sep. 15, 2017.

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi USA, LLC.—Civil Action No. 1:17-cv-01201: Answer to Fresenius Kabi USA, LLC's Counterclaims (Document 14), dated Oct. 6, 2017.

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi USA, LLC.—Civil Action No. 1:17-cv-01201: Complaint (Document 1), dated Aug. 24, 2017.

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi, LLC., et al.—Civil Action No. 1:18-cv-01586: Answer to Fresenius Kabi USA, LLC's Counterclaims (Document 13), dated Nov. 27, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi, LLC., et al.—Civil Action No. 1:18-cv-01586: Complaint (Document 1), dated Oct. 15, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi, LLC., et al.—Civil Action No. 1:18-cv-01586: Defendant Mylan Laboratories LTD.'s Answer to Complaint for Patent Infringement (Document 11), dated Nov. 9, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Fresenius Kabi, LLC., et al.—Civil Action No. 1:18-cv-01586: Defendant Fresenius Kabi USA, LLC's Answer to Complaint, Separate Defenses, and Counterclaims (Document 9), dated Nov. 6, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Mylan Laboratories Limited—Civil Action No. 1:17-cv-01790: Complaint (Document 1), dated Dec. 12, 2017.

Teva Pharmaceuticals International GMBH, et al. v. Mylan Laboratories Limited—Civil Action No. 1:17-cv-01790: Defendant Mylan Laboratories Limited's Answer to Complaint for Patent Infringement (Document 12), dated Feb. 14, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Slayback Pharma Limited Liability Company—Civil Action No. 1:18-cv-00117: Complaint (Document 1), dated Jan. 19, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Slayback Pharma Limited Liability Company—Civil Action No. 1:18-cv-00117: Defendant Slayback Pharma Limited Liability Company's Answer to Complaint, Additional Defenses and Counterclaims (Document 9), dated Feb. 12, 2018.

Teva Pharmaceuticals International GMBH, et al. v. Apotex Inc., et al.—Civil Action No. 1:17-cv-01164: Complaint (Document 1), dated Aug. 18, 2017.

Thiesen, "Bendamustine, a well-tolerated cytotoxic agent used in Germany for many years, is soon to be marketed in the rest of Europe for a range of indications including chronic lymphocytic leukaemia," 2010, pp. 1-4. Available at <http://www.hospitalpharmacyeurope.com/featured-articles/bendamustine>.

Third Party Observation in related EP2528602 based on PCT/US2011/022958 dated Mar. 21, 2016.

Third Party Submission in related EP2528602 based on PCT/US2011/022958 dated Nov. 2013.

Third Party Submission in related EP2528602 based on PCT/US2011/022958 dated Nov. 19, 2013 (9 pages).

Third Party Submission in related EP2528602 dated Nov. 19, 2013. Treanda label, 2008.

Treanda, "Highlights Of Prescribing Information," Treanda bendamustine hydrochloride for Injection, for intravenous infusion, 2008, pp. 1-6.

Treanda, "Highlights of Prescribing Information," Treanda bendamustine hydrochloride for Injection, for intravenous infusion, 2010, pp. 1-13.

Treanda, "Highlights of prescribing information", 2008.

Trivedi et al., "Water-Insoluble Drug Formulation", 7. Solubilization Using Cosolvent Approach, 2000, pp. 141-168.

Trivedi, "Water-Insoluble Drug Formulation", Second Edition, 9 Solubilization Using Cosolvent Approach, 2008, pp. 161-194.

Akers et al., "Excipient-Drug Interactions in Parenteral Formulations", Journal of Pharmaceutical Sciences, Nov. 2002, vol. 91, Issue 11, pp. 2283-2300.

Akers, Remington, The Science and Practice of Pharmacy 21st Edition, Parenteral preparation, chapter 41, 2005, pp. 802-835.

Amdahl et al., Chemistry, 7th Ed., 2007.

American Heart Association, "Living With Heart Failure" (https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/@gwtg/documents/downloadable/ucm_309068.pdf) (2001).

American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin On Hospital Distribution and Control. Am J. Hosp. Pharm. 1980, 37:1097-103.

Amin et al., "Lyophilization of Polyethylene Glycol Mixtures", Journal of Pharmaceutical Sciences 2004, vol. 93, No. 9, pp. 2244-2249.

Armstrong et al., "Separation of Drug Stereoisomers by the Formation of . . . beta-Cyclodextrin Inclusion Complexes", Science, May 1986, vol. 232, pp. 1132-1135.

Baldi et al., "Statistical Procedures for Optimizing the Freeze-Drying of a Model Drug in Tert-Butyl Alcohol: Water Mixtures", Eur. J. of Pharm. & Biopharm., 1994, vol. 40, No. 3, pp. 138-141.

Balfour et al., "Bendamustine", Drugs, 2001, vol. 61, No. 5, pp. 631-638.

Bauer et al., Pharmazeutische Technologies, pp. 225-228, HW9, 1993.

Bauer et al., Pharmazeutische Technologies, pp. 424-425, HW10, 1993.

Bergsagel et al., "Effect of cyclophosphamide on Advanced Lung Cancer and the Hematological Toxicity of Large, Intermittent Intravenous Doses", Canad. Med. Ass. J., 1968, vol. 98, pp. 532-538.

Bernard Testa et al., Hydrolysis in Drug and Prodrug Metabolism, pp. 681-684.

Bernard Testa, et al., "Hydrolysis in Drug and Prodrug Metabolism", Verlag Helvetica Chimica Acta, pp. 681-684, 2003, ISBN 3-906390-25-X.

Biedermann et al., "SciFinder(r) Hydrolytic degradation of IMET", 1969, 3393, vol. 108, pp. 1-2.

Biewenga et al., "The Pharmacology of the Antioxidant Lipoic Acid", Gen. Pharmac., 1997, vol. 29, No. 3, pp. 315-331.

Boylan et al., "Parenteral Products, Chapter 12", Modern Pharmaceutics, Fourth Ed., 2002, pp. 1-34.

Brigitte et al., "Lipoic and Dihydrolipoic Acids . . . , Free Rad". Res., 1994, vol. 20, No. 2, pp. 119-133.

Broadhead et al., "Pharmaceutical Preformulation and Formulation, Chapter 9 in Parenteral Dosage Forms", Interpharm., 2001, pp. 325-347.

Brown, Organic Chemistry 5th Edition, 2009, pp. 358-360.

Canadian Society of Hospital Pharmacists: Guidelines for Drug-Use Control, 2008, pp. 1-28.

Carpenter et al., "A Study of the Polyethylene Glycols as Vehicles for Intramuscular and Subcutaneous Injection", Journal of the American Pharmaceutical Association, 1952, vol. 41, No. 1, pp. 27-29.

Center for Drug Evaluation and Research, Andrew Dmytrijuk, FDA Medical Review for the Approval of Bendeka, 2015, pp. 1-35.

Cephalon, Inc., et al., v. Slayback Pharma Limited Liability Company, et al., Civil Action No. 1:17-cv-01154: Opinion, dated Apr. 27, 2020, 70 pages.

Cephalon, Inc., et al., v. Slayback Pharma Limited Liability Company, et al.—Civil Action No. 1:17-cv-01154: Answer to Slayback Pharma Limited Liability Company's Counterclaims, dated Oct. 20, 2017.

Cephalon, Inc., et al., v. Slayback Pharma Limited Liability Company—Civil Action No. 1:17-cv-01154: Joint Status Report (Document 164), dated Oct. 19, 2018.

Cephalon, Inc., et al., v. Slayback Pharma Limited Liability Company—Civil Action No. 1:17-cv-01154: Complaint (Document 1), dated Aug. 16, 2017.

Cephalon, Inc., et al., v. Slayback Pharma Limited Liability Company—Civil Action No. 1:17-cv-01154: Answer to Slayback Pharma Limited Liability Company's Counterclaims (Document 56), dated Mar. 5, 2018.

US 12,138,248 B2

Page 4

(56)

References Cited

OTHER PUBLICATIONS

- Cerhalon, Inc.*, et al., v. *Slayback Pharma Limited Liability Company*, et al.—Civil Action No. 1:17-cv-01154: Answer to Apotex Inc. and Apotex Corp.’s Counterclaims (Document 22), dated Dec. 18, 2017.
- Cerhalon, Inc.*, et al., v. *Slayback Pharma Limited Liability Company*—Civil Action No. 1:17-cv-00154: Defendant Slayback Pharma Limited Liability Company’s Answer to Complaint and Counterclaims (Document 11), dated Sep. 29, 2017.
- Cerhalon, Inc.*, et al., v. *Slayback Pharma Limited Liability Company*—Civil Action No. 1:17-cv-01154: Joint Claim Construction Chart (Document 94), dated Jul. 24, 2018.
- Chadha et al., “Drug Carrier Systems For Anticancer Agents: A Review”, *Journal of Scientific & Industrial Research*, 2008, vol. 67, pp. 185-197.
- Cheson et al., “Bendamustine: Rebirth of an Old Drug”, *J. Clin. Oncol.*, 2009, vol. 27, pp. 1492-1501.
- Cheung et al., “Safety and Pharmacokinetics of Bendamustine Rapid-Infusion Formulation”, *J. of Clinical Pharmacology*, 2017, vol. 57, No. 11, pp. 1400-1408.
- Chu et al., *Common Chemotherapy Regimens in Clinical Practice*, Physicians’ Cancer Chemotherapy Drug Manual 2009.
- Corbett, *Intravenous Fluids: It’s More Than Just ‘Fill ‘Er Up!’*, Series #52 Practical Gastroenterology, 2007, pp. 44-60.
- Costantino, “Lyophilization Of Biopharmaceuticals”, *Association of Pharmaceutical Scientists*, 2004.
- Cyclobond(R) Handbook, *A Guide to Using Cyclodextrin Bonded Phases for Chiral LC Separations*, 6th ed., 2002, Advanced Separation Technologies, Inc., pp. 1-58.
- Derry et al., “Application of 15N Nuclear Magnetic Resonance Spectroscopy to the Determination of the Stability of Aryl Nitrogen Mustards”, *J. Med. Chem.*, 1995, vol. 38, pp. 2256-2258.
- Draft Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives In the Dossier for Application for Marketing Authorisation of Medicinal Product, EMEA, 2003, pp. 1-10.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01459: Answer to Slayback Pharma LLC’s Counterclaims (Document 13), dated Oct. 31, 2018.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01459: Complaint (Document 1), dated Sep. 20, 2018.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01459: Defendant Slayback Pharma Limited Liability Company’s Answer to Complaint, Additional Defenses, and Counterclaims (Document 9), dated Oct. 10, 2018.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01953: Answer to Slayback Pharma LLC’s Counterclaims (Document 12), dated Jan. 3, 2019.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01953: Complaint (Document 1), dated Dec. 11, 2018.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01953: Defendant Slayback Pharma Limited Liability Company’s Answer to Complaint, Additional Defenses, and Counterclaims (Document 11), public version dated Dec. 20, 2018.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01953: Opening Brief in Support of Slayback Pharma Limited Liability Company’s Motion for Judgment on the Pleadings (Document 17), public version dated Jan. 11, 2019.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01953: Eagle Pharmaceuticals’ Opposition to Slayback Pharma’s Motion for Judgment on the Pleadings (Document 23), redacted—public version dated Feb. 12, 2019.
- Eagle Pharmaceuticals, Inc. v. Slayback Pharma LLC*—Civil Action No. 1:18-cv-01953: Reply Brief in Further Support of Slayback Pharma Limited Liability Company’s Motion for Judgment on the Pleadings (Document 27), public version dated Mar. 1, 2019.
- Eagle Pharmaceuticals, Inc.*, et al. v. *Hospira, Inc.*—Civil Action No. 1:18-cv-01074: Exhibit Index—Includes Confidential Information (Document 21), public version dated Sep. 7, 2018.
- Eagle Pharmaceuticals, Inc.*, et al. v. *Hospira, Inc.*—Civil Action No. 1:18-cv-01074: Complaint (Document 1), dated Jul. 19, 2018.
- Eagle Pharmaceuticals, Inc.*, et al. v. *Hospira, Inc.*—Civil Action No. 1:18-cv-01074: Hospira’s Reply Brief in Support of its Motion to Dismiss Plaintiffs’ Complaint (Document 29), public version dated Nov. 26, 2018.
- Eagle Pharmaceuticals, Inc.*, et al. v. *Hospira, Inc.*—Civil Action No. 1:18-cv-01074: Plaintiffs’ Opposition to Motion to Dismiss (Document 26), redacted—public version dated Nov. 2, 2018.
- EC Safety Data Sheet: Ribomustin(Registered) 2007.
- Eric Watson, et al., *Kinetics of Phosphoramidate Mustard . . .*, *Journal of Pharmaceutical Sciences*, vol. 74, No. 12, pp. 1283-1292, 1985.
- Flamberg et al., “Low Temperature Vacuum Drying of Sterile Parenterals From Ethanol”, *Bulletin of the Parenteral Drug Association*, 1970, vol. 24, No. 5, pp. 209-217.
- Floss et al., “Intravenous fluids principles of treatment”, *Clinical Pharmacist*, 2011, vol. 3, pp. 274-283.
- Friedberg et al., “Bendamustine in Patients with Rituximab-Refractory Indolent and Transformed Non-Hodgkin’s Lymphoma: Results from a Phase II Multicenter, Single-Agent Study”, *J. Clin. Oncol.*, 2008, vol. 26, No. 2, pp. 204-210.
- Friedman et al., “Colorimetric Estimation of Nitrogen Mustards in Aqueous Media. Hydrolytic Behavior of Bis-(β -chloroethyl)amine, nor HN2”, *Analytical Chemistry*, 1961, vol. 33, No. 7, pp. 906-910.
- Fujisawa Deutschland GmbH Ribomustin(Registered) Products and Technical Specifications, 2002.
- Furst et al., “About the Hydrolytic Decomposition of IMET 3393,” *Pharmazeutische Zentralhalle*, 1969, vol. 108, Issue 9, pp. 608-614 (English translation and the original article).
- Galacid Excel 88 fact sheet (lactic acid 88%), 2012.
- Gamcsik et al., “NMR Studies of the Conjugation”, *J. Med. Chem.*, 1990, vol. 33, pp. 1009-1014.
- Gandhi et al., “Bendamustine in B cell malignancies: the new, 46-year old kid on the block”, *Clin Cancer Res.*, 2009, vol. 15, No. 24, pp. 7456-7461.
- Gatlin et al., “Injectable Drug Development”, 17. *Formulation and Administration Products*, pp. 401-420.
- Gibson et al., “Pharmaceutical Preformulation And Formulation: A practical guide from candidate drug selection to commercial dosage form”, *Informa Healthcare USA*, 2009, vol. 199, 2nd ed, pp. 1-559.
- Glimelius et al., “Bolus-Infusion (2-4 min) Versus Short-term (10-20 min) Infusion of 5-Fluorouracil in Patients with Advanced Colorectal Cancer: a Prospective Randomised Trial”, *Eur J. Cancer*, 1998, vol. 34, pp. 674-678.
- Graham Solomons, *Organic Chemistry*, John Wiley & Sons, 3d ed. 1984.
- Gupta et al., “Injectable Drug Development Techniques to Reduce Pain and Irritation”, *Informa Healthcare*, 2008, pp. 183.
- Gust et al., “Investigations on the Stability of Bendamustine, a Cytostatic Agent of the Nitrogen Mustard Type I”, *Synthesis, Isolation, and Characterization of Reference Substances*, in *Monatshefte für Chemie*, 1997, vol. 128, pp. 291-299.
- Handbook of Pharmaceutical Excipients, Seventh edition 2012, Pharmaceutical Press.
- Handbook of Pharmaceutical Excipients, Sixth edition, 2009; Rowe; p. 857 (extract from index).
- Heider et al., “Efficacy and Toxicity of Bendamustine in Patients with Relapsed Low-Grade non-Hodgkin’s Lymphomas”, *Anticancer Drugs*, 2001, vol. 12, pp. 725-729.
- HFSA 2010 Comprehensive Heart Failure Practice Guideline, *Journal of Cardiac Failure*, 2010, vol. 16 No. 6.
- Hsu et al., *Reactions of N-Ethyl-(HN-1), N-Methyl-Bis(2-Chloroethyl)amine (HN-2), and Tris(2-Chloroethyl)amine (HN-3) with Peroxides*, 2002, pp. 1-15.
- ICH Harmonised Tripartite Guideline, *Stability testing of New Drug Substances and Products Q1A(R2)*, dated Feb. 6, 2003.
- Interlocutory decision in Opposition proceedings of EP 2528602 issued Apr. 8, 2019.
- International Conference on Harmonisation in Guideline on Impurities in New Drug Products: Availability, 1997, 62 Fed. Reg. 27, pp. 454-27, p. 461.
- International Search Report and Written Opinion for No. PCT/US2013/032289 dated Jun. 2013.
- International Search Report and Written Opinion issued in counterpart PCT/US2013/032295 dated Jun. 2013 (4 pages).

US 12,138,248 B2

Page 5

(56)

References Cited

OTHER PUBLICATIONS

International Search Report and Written Opinion issued in counterpart PCT/US2013/26187.

International Search Report and Written Opinion of International application based on PCT/US2011/022958, dated Apr. 2011 (8 pages).

International Search Report of International Appln. No. PCT/US2013/032289 mailing date Jun. 6, 2013.

International Search Report PCT/US2011/022958 dated Apr. 12, 2011.

Jennings, "Lyophilization, Introduction and Basic Principles", 2006, original copyright 1999.

Jerry, Advanced Organic Chemistry, 4th ed., John Wiley & Sons, Inc. 1992.

Jones, "Applications of Hydrogen Peroxide and Derivatives", Royal Society of Chemistry, 1999, 1 page.

Jonkman-De Vries et al., "Pharmaceutical Development of (Investigational) Anticancer Agents for Parental Use—A Review", Drug Dev Ind Pharm. 1996, vol. 22, No. 6, pp. 475-494.

Kalaycio, "Clinical Experience With Bendamustine: A New Treatment for Patients With Chronic Lymphocytic Leukemia", Clin Leukemia., 2008, vol. 2, No. 4, pp. 223-229.

Kenneth et al., "Remington, Parenteral Preparations", Chapter 41, 2000, pp. 780-786.

Knauf et al., "Bendamustine Versus Chlorambucil in Treatment-Naive Patients with B-Cell Chronic Lymphocytic Leukemia (B-CLL): Results of an International Phase III Study", Blood, 2007, vol. 110, No. 11, 609a.

Koomans et al., "Sodium Balance in Renal Failure: A Comparison of Patients with Normal Subjects Under Extremes of Sodium Intake", Hypertension, 1985, vol. 7, pp. 714-721.

Kumar et al., AAPS Pharm Sci Tech., 2006, vol. 7, No. 3, pp. E1-E7.

Leonard et al., A New Synthesis of Aziridinium Salts. 2,2-Pentamethylene-1,1-tetramethyleneaziridinium Perchlorate A Prototype, J. Am. Chemistry Soc'y, 1960, vol. 82, pp. 6418-6419.

Leoni et al., "SDX-105 (Bendamustine), a Clinically Active Antineoplastic Agent Possesses a Unique Mechanism of Action", Blood, 2003, vol. 102, No. 11, Abstract #2363.

Lian-Feng et al., "Water-Insoluble Drug Formulation", Second Edition, Ch. 7. Formulation Strategies and Practice. Support, pp. 113-132.

Lissitchkov et al., Phase-I/II study to Evaluate Dose Limiting Toxicity, Maximum Tolerated Dose, and Tolerability of Bendamustine HCl in Pre-treated Patients With B-Chronic Lymphocytic Leukemia (Binet stages B and C) Requiring Therapy, J. Cancer Res. Clin. Oncol. 2006, vol. 132, pp. 99-104.

Liu (ed). Water-Insoluble Drug Formulation, 1st ed., CRC Press, Chapters 7 and 9, 2000.

Liu (ed). Water-Insoluble Drug Formulation, 2nd ed., CRC Press, Chapters 7 and 9, 2000.

Lyondell Tebol (Registered) 99, Tertiary Butyl Alcohol in Freeze-Drying Applications, Lyondell Chemical Co., 2003.

Maas B: "Stabilität von Bendamustinehydrochlorid in Infusionslösungen" Die Pharmazie, Govi Verlag Pharmazeutischer Verlag GmbH, Eschborn, DE, vol. 49, No. 10, Jan. 1, 1994.

Maas et al., "Stabilität von Bendamustinehydrochlorid in Infusionslösungen," Die Pharmazie, Govi Verlag Pharmazeutischer Verlag GmbH, vol. 49, No. 10 pp. 775-777 (1994). (Abstract Only).

Maas, "Stabilität von Bendamustinehydrochlorid in Infusionslösungen", Die Pharmazie, Govi Verlag Pharmazeutischer Verlag GmbH, Eschborn, DE, 1994, vol. 49, No. 10, pp. 775-777.

Margolin et al., "Shortening the Infusion Time of Anticancer Drugs: Who Will Benefit?", J. of Clinical Oncology, 2007, vol. 25 No. 19, pp. 2642-2643.

Meginity et al., "Influence of Peroxide Impurities in Polyethylene Glycols", Journal of Pharmaceutical Sciences, 1975, vol. 64, No. 2, pp. 356-357.

Mikhail'chuk et al., "Antioxidative Stabilization of Polyethylene . . .", Russian Journal of Applied Chemistry, 2004, vol. 77, No. 1, pp. 131-135.

National Kidney Foundation, "Clinical Practice Guidelines and Clinical Practice Recommendations" http://kidneyfoundation.cachefly.net/professionals/KDOQI/guideline_upHD_PD_VA/hd_guide5.htm, 2006.

Nema et al., "Excipients and Their Use in Injectable Products", PDA J. Pharma. Sci. & Tech., 1997, vol. 51, No. 4, pp. 166-171.

Nema et al., "Excipients and Their Use in Injectable Products", PDA Journal of Pharmaceutical Science & Technology, May 16, 1997.

Ni et al., "Stabilization and Preformulation of Anticancer Drug-SarCNU", Int'l J. of Pharma., 2002, vol. 249, No. 257-264.

Ni et al., "Use of pure t-butanol as a solvent for freeze-drying: a case study", International Journal of Pharmaceutics, 2001, vol. 226, pp. 39-46.

Ni et al., Use of Pure t-Butanol as a Solvent for Freeze-Drying: A Case Study, Int'l. J. of Pharma., 226:39-46 (2001).

Nuijen et al., "Pharmaceutical Development of a Parenteral Lyophilized Formulation of the Novel Antitumor Agent Aplidine", PDA J. Pharmaceut. Sci. and Technol., 2000, vol. 54, No. 3, pp. 193-208.

O'Connor, "Hydrolysis and Alkylating Reactivity of Aromatic Nitrogen Mustards", J.Chem. Soc. Perkin Trans., 1991, vol. 2, pp. 1933-1939.

Olson, "Volatile Solvents for Drying and Microbial Kill in the Final Container", Pharmaceutical Engineering, 1997, pp. 110-118.

Olthoff et al., OlthoffT, DD 159289, cited in IDS filed Jan. 24, 2014.

Ozegowski et al., "IMET 3393, ?-[1-Methyl-5-bis-(Beta-chloroethyl)-amino-benzimidazolyl-(2)]-butyric acid hydrochloride, a new cytostatic agent from the benzimidazole mustard gas series", 110 Zbl Pharm. 1971, vol. 110, pp. 1013-1019.

PCT Notification of Transmittal of International Search Report and Written Opinion for PCT/US2013/032295.

PCT Written Opinion of International Search Authority for PCT/US2013/032295.

Pethrick et al., Excerpt from Polymer Yearbook 13, CRC Press, Oct. 1, 1996, Technology & Engineering Vinogradova et al.

Pokorny et al., "Antioxidants in Food: Practical Applications", CRC Press, 2001, p. 324.

Poulsen, Introduction to Chemistry (2010).

Pramod K. Gupta Injectable Drug Development Techniques to Reduce pain and irritation.

Preiss et al., "Pharmacological and clinical data of Bendamustine," 17th International Cancer Congress, 1998, pp. 1637-1640.

Preiss et al., "Studies on the Pharmacokinetics of Bendamustine (Cytostasan®) in Humans", Pharmazie, 1985, vol. 40, No. 11, pp. 782-784.

Price, Handbook of Pharm. Excipients, 5th Edition, "Polyethylene Glycol", Aug. 2005, pp. 545-550.

Qin et al., "Oxidative degradation of oligo(ethylene glycol)-terminated monolayers", Chem. Commun. 2009, pp. 5112-5114.

Rassachaert et al., "A phase 1 study of bendamustine hydrochloride administered once every 3 weeks in patients with solid tumors," Anti-Cancer Drugs, 2007, vol. 18 No. 5, pp. 587-595.

Ready-to-Use [online] retrieved on May 27, 2021 from: <https://medical-dictionary.thefreedictionary.com/ready-to-use>; 2021, 1 page.

Remington's Pharmaceutical Sciences, 18th edition, (1990), p. 1322.

Remington's Pharmaceutical Sciences, 18th edition, (1990), pp. 1286-1288.

Remington's Pharmaceutical Sciences 1990 (Eighteenth Edition), Mack Publishing Company, Chapter 85, pp. 1570-1580.

Ribomustin Monograph (Updated Aug. 2005).

Ribomustin Monograph (Updated Jan. 2002).

Ribomustin Product Information, Janssen-Cilag Pty Ltd (Updated Sep. 15, 2016).

Roberts et al., Basic Principles Of Organic Chemistry, W. A. Benjamin, Inc., 2d ed. 1977, pp. 612-618.

Rote Liste 1996 for Ribomustin (86 023).

Rote Liste 2003 for Ribomustin (86 045).

Rowe et al. Handbook of Pharmaceutical Excipients, 6th edition, 2009, pp. 454-455.

Rowe et al., "Handbook of Pharmaceutical Excipients," Pharmaceutical Press, 6th edition pp. 857 (extract from index) (2009).

US 12,138,248 B2

Page 6

(56)

References Cited

OTHER PUBLICATIONS

Rowe et al., Handbook of Pharmaceutical Excipients, 5th ed., Pharmaceutical Press, pp. 545-550, Polyethylene Glycol, 2006.
Safety Data Sheet, Lactic Acid, 88%, Colu{acute over (m)}bus Chemical Industries, 2013.

Safety Data Sheet, Lactic Acid, 88%, Columbus Chemical Industries, 2013.

Santacesaria et al., "Thermal Stability Of Nonionic Polyoxyalkylene Surfactants", Journal of Applied Polymer Science, 1991, vol. 42, pp. 2053-2061.

Scasnar et al., "Radiochemical Assay of Stability of ¹⁴C-Cytostasan Solutions During Preparation and Storage", Journal of Radioanalytical and Nuclear Chemistry, Articles, 1988, vol. 121, No. 2, pp. 489-497.

Schoffski et al., "Weekly Administration of Bendamustine: A phase I study in patients with advanced progressive solid tumors", Annals of Oncology II, 2000, pp. 729-734.

Schoffski et al., "Repeated administration of short infusions of bendamustine: a phase I study in patients with advanced progressive solid tumours", J. Cancer Res Clin Oncol, 2000, vol. 126 No. 1 pp. 41-47.

Schwanen et al., "In vitro evaluation of bendamustine induced apoptosis in B-chronic lymphocytic leukemia", Leukemia, 2002, vol. 16, pp. 2096-2105.

U.S. Appl. filed Dec. 5, 2013., U.S. Appl. No. 14/097,904.

U.S. Appl. filed Dec. 5, 2013., U.S. Appl. No. 14/098,094.

U.S. Appl. filed Feb. 14, 2013., U.S. Appl. No. 13/767,672.

U.S. Appl. filed Nov. 26, 2014., U.S. Appl. No. 14/554,269.

U.S. Appl. filed Oct. 23, 2014., U.S. Appl. No. 14/522,581.

U.S. Appl. filed Sep. 19, 2013., U.S. Appl. No. 14/031,879.

U.S. Pharmacopeia 32-NF-27-General Notices and Requirements, 2009.

U.S. Appl. No. 10/010,533, filed Dec. 7, 2001.

U.S. Appl. No. 10/052,385, filed Jan. 18, 2002.

U.S. Appl. No. 16/015,656, filed Jun. 22, 2018.

USP 24/NF 19 (2000) entry for Propylene Glycol (USP).

Vinogradova et al., "New Metal Chelates as Antioxidant Stabilizers for Polymers . . .", Polymer Yearbook 13, pp. 87-111, 1996.

Vlok, Manual of Nursing, 1988m vol. 1, 9th edition.

Wasyilaschuk et al., Journal Of Pharmaceutical Sciences, 2007, vol. 96, No. 1, pp. 106-116.

Waterman et al., "Stabilization of Pharmaceuticals to Oxidative Degradation", Pharmaceutical Development and Technology, 2002, vol. 7, No. 1, pp. 1-32.

Watson et al., "Kinetics of phosphoramidate mustard hydrolysis in aqueous solution", Journal of Pharmaceutical Sciences, 1985, vol. 74, Issue 12, pp. 1283-1292.

Weide et al., "Bendamustine Mitoxantrome and Rituximab (BMR): A New Effective Regimen for Refractory or Relapsed Indolent Lymphomas", Leukemia & Lymphoma, 2002, vol. 43, No. 2, pp. 327-331.

Werner et al., Hydrolysis Products of Cancerostatic Cytostasan(Registered) (Bendamustine), 42 (4) Die Pharmazie, Govi Verlag Pharmazeutischer Verlag GMBH, Eschborn, DE, 272-73.

Wittaya-Areekul et al., "Freeze-Drying of tert-Butyl Alcohol/Water Cosolvent Systems: Effects of Formulation and Process Variables on Residual Solvents", Journal of Pharmaceutical Sciences, 1998, vol. 87, No. 4, pp. 491-495.

Written Opinion issued in counterpart PCT/US2013/032289 dated Jun. 6, 2013.

Written Opinion issued in counterpart PCT/US2013/032295 dated Jun. 3, 2013.

Written Opinion of the International Searching Authority re: International Appln. No. PCT/US2013/032289 mailing date Jun. 6, 2013.

Zimmerman et al., Elements of Organic Chemistry, 1977.

Zips et al., "New Anticancer Agents: In Vitro and In Vivo Evaluation," In Vivo, 2005, vol. 19, pp. 1-8.

Zumdahl et al., Chemistry, 7th Ed., 2007.

* cited by examiner

US 12,138,248 B2

1

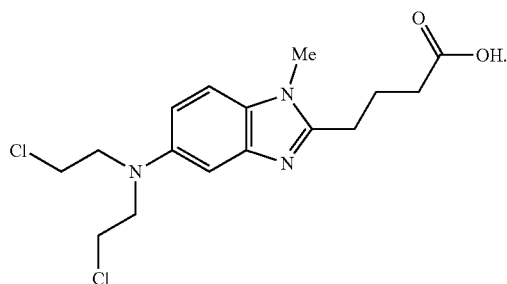
FORMULATIONS OF BENDAMUSTINE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 18/498,259, filed Oct. 31, 2023, which is a continuation of application Ser. No. 16/509,920, filed Jul. 12, 2019, now U.S. Pat. No. 11,103,483, which is a continuation of application Ser. No. 16/015,656, filed Jun. 22, 2018, which is a continuation of application Ser. No. 15/432,335, filed Feb. 14, 2017, now U.S. Pat. No. 10,010,533, issued Jul. 3, 2018, which is a continuation of application Ser. No. 15/013,436, filed Feb. 2, 2016, now U.S. Pat. No. 9,572,797, issued Feb. 21, 2017, which is a continuation of application Ser. No. 14/031,879, filed Sep. 19, 2013, now U.S. Pat. No. 9,265,831, issued Feb. 23, 2016, which is a continuation of application Ser. No. 13/016,473, filed Jan. 28, 2011, now U.S. Pat. No. 8,609,707, issued Dec. 17, 2013, which claims the benefit of U.S. Provisional Patent Application No. 61/299,100, filed Jan. 28, 2010, the contents of each of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Bendamustine free base is represented by the following structural formula (I)



Bendamustine is used in the treatment of a number of cancers including leukemias, Hodgkins disease and multiple myelomas. Bendamustine is the active ingredient of the commercial product Treanda™, a lyophilized powder for reconstitution.

Bendamustine exhibits rapid degradation upon reconstitution of the lyophilized product. Bendamustine undergoes hydrolysis by direct substitution rather than an addition elimination process due to the presence of the highly labile aliphatic chlorine atoms. Some of the main degradants of bendamustine are the monohydroxy compound known as HP1 (hydrolysis product 1) and dihydroxy compound HP2 (hydrolysis product 2). The monohydroxy compound appears as the main impurity at Relative Retention Time (RRT) 0.6 and the dihydroxy compound appears as the main impurity at RRT 0.27. Minor peaks appear at RRT 1.2, which are presently unknown.

The stability of bendamustine in water is measured in hours, and is therefore, not suitable for long-term storage in liquid form. The lyophile possesses good chemical stability. However, reconstitution of the lyophile is clinically inconvenient, taking 15-30 mins with implications of chemical instability. There is a need for ready to use (RTU) bendamustine formulations having enhanced stability.

2

SUMMARY OF THE INVENTION

In other aspects of the invention, the bendamustine-containing compositions include a) a pharmaceutically acceptable fluid which contains one or more of propylene glycol, ethanol, polyethylene glycol, benzyl alcohol and glycofurol, and b) a stabilizing amount of a chloride salt. In other aspects of the invention, the bendamustine-containing compositions include DMSO (dimethyl sulfoxide) as part of the pharmaceutically acceptable fluid included therein. Regardless of the pharmaceutically acceptable fluid included, the amount of bendamustine included in the composition is preferably from about 20 mg/mL to about 60 mg/mL. Still further aspects of the invention include methods of treatment using bendamustine-containing compositions and kits containing the same.

One of the advantages of the inventive liquid compositions is that they have substantially improved long term stability when compared to currently available formulations. For example, the inventive bendamustine compositions are substantially free of impurities after at least about 15 months at a temperature of from about 5° C. to about 25° C. The inventive formulations are advantageously ready to use or ready for further dilution. Reconstitution of lyophilized powders is not required.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, RRT is calculated by dividing the retention time of the peak of interest by the retention time of the main peak. Any peak with an RRT<1 elutes before the main peak, and any peak with an RRT>1 elutes after the main peak.

For purposes of the present invention, "substantially free of impurities" shall be understood to include bendamustine-containing compositions in which the amount of total impurities is less than about 5%, as calculated on a normalized peak area response ("PAR") basis as determined by high performance liquid chromatography ("HPLC") at a wavelength of 223 nm, after a period of about 15 months at a temperature of from about 5° C. to about 25° C. The amount of impurities is further calculated as being based upon the original amount bendamustine (or salt thereof) being present in the composition or formulation.

For purposes of the present invention, a pharmaceutically acceptable fluid is a fluid which is suitable for pharmaceutical use.

Preferably, the amount of any individual degradant in the inventive compositions does not exceed 2% PAR as determined by HPLC at a wavelength of 223 nm after storage periods of at least about 15 months at a temperature of from about 5° C. to about 25° C. In some aspects, the amount of time the inventive compositions demonstrate long term storage stability is at least about 18 months and preferably at least about 2 years when stored under the conditions described herein.

In accordance with one aspect of the invention there are provided long term storage stable bendamustine-containing compositions including:

US 12,138,248 B2

3

- a) bendamustine or a pharmaceutically acceptable salt thereof; and
- b) a pharmaceutically acceptable fluid including
 - i) PEG, PG or mixtures thereof; and
 - ii) a stabilizing amount of an antioxidant.

The total impurities in the inventive compositions resulting from the degradation of the bendamustine in the compositions is less than about 5% PAR as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of from about 5° C. to about 25° C., and thus have long term stability for at least the same period of time or longer. Preferably, the bendamustine-containing compositions demonstrate long term storage stability for at least about 2 years, especially when stored at the lower (refrigerated) temperatures. In one embodiment, the amount of total impurities in the inventive compositions resulting from the degradation of the bendamustine is less than about 3% PAR as determined by HPLC at a wavelength of 223 nm after at least about 2 years at a temperature of from about 5° C. to about 25° C.

In some aspects of the invention, the bendamustine concentration in the inventive compositions is from about 10 mg/mL to about 100 mg/mL, preferably 20 mg/mL to about 60 mg/mL. Preferably the bendamustine concentration in the inventive compositions is from about 25 mg/mL to about 50 mg/mL, and more preferably from about 30 mg/mL to about 50 mg/mL. It will be understood that compositions containing any useful concentration within the ranges, i.e. 10, 20, 25, 30, 35, 40, 45, 50, 55, 60 . . . 100 are contemplated. In other embodiments, the bendamustine concentration in the composition is about 50 mg/mL. In alternative aspects, the amount of bendamustine is outside these ranges but the amounts will be sufficient for single or multiple administrations of dosages generally regarded as effective amounts.

In several embodiments of the invention, pharmaceutically acceptable fluid is non-aqueous and may be, but is not necessarily, a solvent for the bendamustine or salt thereof. Within this aspect, the pharmaceutically acceptable fluid is propylene glycol (PG) or polyethylene glycol (PEG). In other embodiments of the invention however, the pharmaceutically acceptable fluid is a mixture of PEG and PG. For example, the pharmaceutically acceptable fluid can include about 50% PEG and about 50% PG. Alternatively, pharmaceutically acceptable fluid includes about 95% PEG and about 5% PG. The amount of PEG and PG can also be varied within the ranges, i.e. the ratio of PEG:PG in the pharmaceutically acceptable fluid can range from about 95:5 to about 50:50. Within this range, is a pharmaceutically acceptable fluid containing about 75% PEG and about 25% PG, and preferably 80% PEG and 20% PG. In another embodiment, a pharmaceutically acceptable fluid can include about 85% PEG and about 15% PG while another preferred pharmaceutically acceptable fluid includes about 90% PEG and about 10% PG. The molecular weight of the PEG will be within the range of pharmaceutically acceptable weights although PEG 400 is preferred in many aspects of the invention.

Without meaning to be bound by any theory or hypothesis, the hydroxide of the polyethylene glycol molecule is less reactive than the hydroxides of propylene glycol. As a result, the ester forms at a slower rate in polyethylene glycol than propylene glycol and the resulting bendamustine degradants are unexpectedly and substantially reduced over extended periods of time when PEG is a substantial part of the pharmaceutically acceptable fluid.

The bendamustine-containing compositions according to several preferred aspects of the invention include a stabiliz-

4

ing amount of an antioxidant. For purposes of the present invention, "stabilizing amount" shall be understood to include those amounts which increase or enhance the stability of the bendamustine in the compositions described herein. The presence of one or more antioxidants described herein thus contributes, at least in part to the long term stability of the composition. Within this guideline, suitable antioxidant concentrations in the compositions can range from about 2.5 mg/mL to about 35 mg/mL, and preferably from about 5 mg/mL to about 20 mg/mL or from about 10 mg/mL to about 15 mg/mL. In some other embodiments, the concentration of the antioxidant in the bendamustine-containing composition is about 5 mg/mL.

Suitable antioxidants for inclusion include those which are pharmaceutically acceptable for use in human and veterinary formulations although not limited to those currently regarded as safe by any regulatory authority. For example, the antioxidant can be selected from among lipoic acid, thioglycerol (also known as monothioglycerol) and analogs thereof, propyl gallate, methionine, cysteine, metabisulfites, sodium formaldehyde sulfoxylate, phenol-containing aromatic and aliphatic compounds, dihydrolipoic acid and mixtures of the foregoing. Preferably, the antioxidant is thioglycerol, lipoic acid or a mixture thereof. Some particularly preferred embodiments of the invention include thioglycerol.

In view of the foregoing, some preferred long term storage stable bendamustine-containing compositions in accordance with the invention compositions include:

- I. a) bendamustine or a pharmaceutically acceptable salt thereof; and
- b) a pharmaceutically acceptable fluid including
 - i) polyethylene glycol and propylene glycol; and
 - ii) a stabilizing amount of thioglycerol; or
- II. a) about 50 mg/mL bendamustine or a pharmaceutically acceptable salt thereof; and
- b) a pharmaceutically acceptable fluid including
 - i) about 90% PEG and about 10% PG; and
 - ii) about 2.5 mg/mL thioglycerol.

Each of these compositions have the same stability profiles already described, i.e. having less than about 5% total impurities, PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

In accordance with other aspects of the invention, there are provided long term storage stable bendamustine-containing compositions, including:

- a) bendamustine or a pharmaceutically acceptable salt thereof;
- b) a pharmaceutically acceptable fluid including one or more of the following: PG, ethanol, PEG, benzyl alcohol and glycofurol; and
- c) a stabilizing amount of a chloride salt.

These compositions also have the low levels of impurities and long term stability mentioned herein. Preferred pharmaceutically acceptable fluids include PG, PEG or ethanol in this embodiment of the invention. Preferably, the PEG is PEG 400. If desired, glycerin and/or 88% (w/w) lactic acid can be added to the pharmaceutically acceptable fluid.

Suitable chloride salts include but are not limited to organic chloride salts, sodium chloride, choline chloride, hydrochloride salts of amino acids and mixtures thereof. Thus, as will be appreciated by those of ordinary skill, one can select from among a number of suitable chloride salts and it is Applicants' intention that the scope of the invention includes all such chloride salts that are capable of being included in bendamustine-containing formulations for

US 12,138,248 B2

5

extended periods without having a deleterious effect on the drug. In one embodiment of the invention, the chloride salt concentration is from about 10 to about 300 mg/mL. In another embodiment, the chloride salt concentration is from about 50 to about 215 mg/mL. In one preferred embodiment, the chloride salt concentration is about 215 mg/mL.

In accordance with another aspect of the invention, there is provided long term storage stable bendamustine-containing compositions, including:

- a) bendamustine or a pharmaceutically acceptable salt thereof; and
- b) a pharmaceutically acceptable fluid including DMSO.

These compositions also have the low levels of impurities and long term stability mentioned herein. In some aspects, the bendamustine concentration in these compositions is from about 10 mg/mL to about 100 mg/mL. Preferably, the bendamustine concentration is from about 20 mg/mL to about 50 mg/mL, more preferably from about 25 mg/mL to about 50 mg/mL. In an alternative embodiment, the bendamustine concentration is about 50 mg/mL.

Another embodiment of the invention provides methods of treating cancer in mammals. The methods include administering to a mammal in need thereof an effective amount of one of the bendamustine-containing compositions described herein. Since the active ingredient portion of the inventive composition is an FDA-approved drug, those of ordinary skill will recognize that the doses of bendamustine employed in this aspect of the invention will be similar to those employed in any treatment regimens designed for bendamustine as marketed under the trade name TRE-ANDA. The patient package insert containing dosing information is incorporated herein by reference. The methods of treatment also include administering the inventive formulations for any purpose or physical condition for which bendamustine has been indicated as being useful.

Another embodiment of the invention includes methods of preparing bendamustine-containing compositions described herein. The methods include reconstituting lyophilized bendamustine in a pharmaceutically acceptable fluid containing one of the following:

- A) i) PEG, PG or mixtures thereof; and
- ii) a stabilizing amount of an antioxidant;
- B) i) one or more of PG, ethanol, PEG, benzyl alcohol and glycofurol; and
- ii) a stabilizing amount of a chloride salt; or
- C) DMSO.

The steps are carried out under pharmaceutically acceptable conditions for sterility and manufacturing.

In a further aspect of the invention, there are provided methods of controlling or preventing the formation of impurities in bendamustine-containing compositions during long term storage. The methods include combining an amount of bendamustine or a pharmaceutically acceptable salt thereof with a sufficient amount of a pharmaceutically acceptable fluid containing one of the following:

- A) i) PEG, PG or mixtures thereof; and
- ii) a stabilizing amount of an antioxidant;
- B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and
- ii) a stabilizing amount of a chloride salt; or
- C) DMSO.

Further optional steps in accordance therewith include transferring one or more pharmaceutically acceptable doses of the formulations into a suitable sealable container and storing the sealed container at a temperature of from about 5° C. to about 25° C. As a result of carrying out these steps, it is possible to control or substantially prevent the formation

6

of impurities which otherwise occur with bendamustine-containing compositions during long term storage so that the artisan is provided with bendamustine-containing formulations having less than about 5% total impurities PAR as determined by HPLC at a wavelength of 223 nm, after at least about 15 months of storage at a temperature of from about 5° C. to about 25° C.

The compositions of the present invention can be packaged in any suitable sterile vial or container fit for the sterile storage of a pharmaceutical such as bendamustine. Suitable containers can be glass vials, polypropylene or polyethylene vials or other special purpose containers and be of a size sufficient to hold one or more doses of bendamustine.

A further aspect of the invention includes kits containing lyophilized bendamustine or a pharmaceutically acceptable salt thereof in a first container or vial; and, in a second container, a sufficient amount of a pharmaceutically acceptable fluid such as those described herein, i.e. one of the following:

- A) i) PEG, PG or mixtures thereof; and
- ii) a stabilizing amount of an antioxidant;
- B) i) one or more of PG, ethanol, PEG, glycofurol and benzyl alcohol; and
- ii) a stabilizing amount of a chloride salt; or
- C) DMSO.

For purposes of this embodiment, the amount of fluid which is sufficient is an amount which allows the bendamustine to be dissolved or dispersed to a degree which renders the liquid composition ready for use.

As will be appreciated by those of ordinary skill, the kit will contain other pharmaceutically necessary materials for storing and/or administering the drug, including instructions for storage and use, additional diluents, if desired, etc.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention.

Example 1

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10 mg/ml in one of ethanol, propylene glycol and benzyl alcohol as indicated in Table 1 below. 215 mg/ml of choline chloride was added in half of the samples as a source of soluble chloride ions. The samples were maintained at 40° C. and analyzed periodically for drug content and total impurities. The results obtained are presented in Table 1.

TABLE 1

Stability of Bendamustine HCl

Formulation	Temp	Time	BDM mg/ml	% Total Impurities
BDM - 10 mg/mL	40° C.	Initial	10.43	0.27
Choline chloride - 215 mg/mL		48 hrs	10.48	1.27
Ethanol qs to 1 mL		7 day	10.26	2.11
BDM - 10 mg/mL	40° C.	Initial	10.55	0.27
Ethanol qs to 1 mL		48 hrs	10.30	2.39
		7 day	9.55	6.66
BDM - 10 mg/mL	40° C.	Initial	9.99	0.21
Choline chloride - 215 mg/ml		48 hrs	9.95	0.60
Propylene glycol qs		7 day	9.43	2.31

US 12,138,248 B2

7

TABLE 1-continued

Stability of Bendamustine HCl				
Formulation	Temp	Time	BDM mg/ml	% Total Impurities
to 1 mL				
BDM - 10 mg/mL		Initial	9.68	0.21
Propylene glycol qs	40° C.	48 hrs	9.45	0.88
to 1 mL		7 day	9.00	3.44
BDM - 10 mg/mL		Initial	9.95	1.19
Choline Chloride -	40° C.	48 hrs	9.89	3.51
215 mg/mL		7 day	8.97	4.24
Benzyl alcohol qs				
to 1 mL				
BDM - 10 mg/mL		Initial	9.52	0.33
Benzyl alcohol qs	40° C.	48 hrs	8.67	4.18
to 1 mL		7 day	7.49	7.84

Note:

In Table 1 the total % impurities include total contributions from peaks at various RRTs.

As shown in Table 1, the bendamustine formulations are very stable in solutions containing solvent and chloride salt. Table 1 shows that bendamustine, when dissolved at a concentration of about 10 mg/mL, in a pharmaceutically acceptable fluid, such as ethanol and propylene glycol, and containing a stabilizing amount of a chloride salt, such as choline chloride, had less than about 5% after at least 7 days storage at 40° C.

The data presented in Table 1 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of a chloride salt having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including ethanol alone exhibited more than 6.5 total degradants after 7 days storage at 40° C. The sample including benzyl alcohol alone exhibited more than 7.5% total degradants after 7 days storage at 40° C. Bendamustine-containing compositions with such high levels of degradation would not be suitable for long-term storage.

Example 2

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 10 mg/ml in DMSO. The samples were maintained at 40° C. and analyzed periodically for drug content and impurity profile. The results obtained are presented in Table 2.

TABLE 2

Stability of Bendamustine HCl in DMSO				
Formulation	Temp	Time	Content (mg/mL)	% Total Imp
BDM - 10 mg/mL		Initial	10.2	0.23
DMSO qs to 1 mL	40° C.	48 hrs	9.80	0.30
		1 week	10.0	0.56

Note:

In Table 2 the total % impurities include total contributions from peaks at various RRTs.

8

Table 2 shows that bendamustine, when dissolved in DMSO, had substantially no increase in total degradants. The data presented in Table 2 translates to bendamustine-containing compositions including DMSO having a shelf life of at least about 15 months at 5° C. and 25° C. In fact, such compositions are expected to have long term stability for periods beyond 15 months, i.e. up to 2 years or greater.

Example 3

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 20 mg/ml in polyethylene glycol 400 and 5 mg/ml of lipoic acid was added as a stabilizing antioxidant as indicated in Table 3 below. The samples were maintained at 40° C. or 25° C. and analyzed after 15 days for drug content and impurities. The results obtained are presented in Table 3.

TABLE 3

Stability of Bendamustine (20 mg/ml) in PEG 400 and Antioxidants					
Antioxidant	T ° C.	Time days	% Initial	% Imp RRT 0.58	% Total Imps
None	25	15	97.6	2.08	2.28
	40	15	56.3	2.17	41.9
Lipoic Acid	25	15	98.5	<LD	0.23
5 mg/ml	40	15	97.5	0.33	0.53

<LD = Below Level of Detection

As shown in Table 3, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as polyethylene glycol, in the presence of a stabilizing amount of an antioxidant, such as lipoic acid, had substantially no increase in total degradants after a period of 15 days. The data presented in Table 3 translates to bendamustine-containing compositions including a pharmaceutically acceptable fluid and a stabilizing amount of an antioxidant having a shelf life of at least about 15 months at 5° C. and 25° C.

The sample including PEG alone, on the other hand, which did not contain an antioxidant, did not exhibit stabilizing effects at 40° C. This sample had more than 40% more total impurities than the sample including lipoic acid. Bendamustine-containing compositions with such high levels of total impurities would not be suitable for long-term storage.

Example 4

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 5 mg/ml of thioglycerol, α -lipoic acid or dihydro-lipoic acid was added as a stabilizing antioxidant as indicated in Table 4 below. The samples were maintained at 40° C. and analyzed after 15 days or one month for drug content and impurity profile as indicated in Table 4 below. The results obtained are presented in Table 4.

US 12,138,248 B2

9

10

TABLE 4

Stability of Bendamustine (50 mg/ml) in 90% PEG 400, 10% Propylene Glycol and Antioxidant							
Antioxidant	T (° C.)	Time	Content (mg/mL)	% Initial	% Impurities RRT		% Total Imps
					HP1 0.59	PG ester 1.10	
Thioglycerol	40	initial	48.8	100	<LD	<LD	0
	40	1 month	48.5	99.4	0.06	0.20	0.71
α -lipoic acid	40	initial	49	100	<LD	<LD	0
	40	15 days	48.8	99.6	0.19	0.13	0.32
	40	1 month	48.7	99.4	0.34	0.26	0.79
Dihydrolipoic acid	40	initial	49.3	100	<LD	<LD	0
	40	1 month	47.7	97.4	0.63	0.12	1.84

<LD = Below Level of Detection

As shown in Table 4, bendamustine, when dissolved in a pharmaceutically acceptable fluid, such as a combination of polyethylene glycol and propylene glycol, in the presence of

after 1 week, 15 days or one month for drug content and impurity profile as indicated in Table 5 below. The results obtained are presented in Table 5.

TABLE 5

Stability of Bendamustine (50 mg/ml) and Lipoic Acid (5 mg/ml) in PEG400 and Propylene glycol								
Formulation	Temp.	Time Period	Content (mg/mL)	% of Initial	% Area of degradants			% Total Imp.
					HP1 0.58	PG ester 1.10	PG ester 1.13	
BDM - 50 mg/mL	40° C.	Initial	49.6	100	BDL	BDL	BDL	0.18
Lipoic acid- 5 mg/mL		1 W	49.0	98.8	0.05	0.13	BDL	0.38
		15 d	48.3	97.4	0.08	0.26	BDL	0.55
PEG	25° C.	1 M	48.0	96.8	0.11	0.43	0.13	1.03
400:PG		15 d	49.6	100.0	BDL	0.10	BDL	0.30
(75:25) qs	5° C.	1 M	48.4	97.6	0.05	0.19	BDL	0.43
to 1 mL		1 M	49.6	100.0	BDL	0.07	BDL	0.27
BDM- 50 mg/mL	40° C.	Initial	50.2	100	BDL	BDL	BDL	0.21
Lipoic acid- 5 mg/mL		1 W	49.9	99.4	BDL	0.15	BDL	0.30
		15 d	49.1	97.8	0.06	0.35	BDL	0.73
PEG	25° C.	1 M	49.0	97.6	0.09	0.90	0.25	1.82
400:PG		15 d	49.9	99.4	BDL	0.12	BDL	0.32
(50:50) qs	5° C.	1 M	49.7	99.0	BDL	0.25	BDL	0.59
to 1 mL		1 M	50.0	99.6	BDL	0.11	BDL	0.33
BDM- 50 mg/mL	40° C.	Initial	50.8	100	BDL	BDL	BDL	0.21
Lipoic acid- 5 mg/mL		1 W	50.4	99.2	BDL	0.11	BDL	0.30
		15 d	49.7	97.8	0.07	0.17	BDL	0.43
PEG	25° C.	1 M	49.7	97.8	0.13	0.27	0.09	0.84
400:PG		15 d	50.8	100.0	BDL	0.10	BDL	0.26
(90:10) qs	5° C.	1 M	50.8	100.0	0.05	0.14	BDL	0.39
to 1 mL		1 M	50.8	100.0	BDL	0.06	BDL	0.34

BDL = Below Detectable Limit

a stabilizing amount of an antioxidant, such as thioglycerol, α -lipoic acid or dihydrolipoic acid, had substantially no increase in total degradants after a period of 1 month. This data supports the position that bendamustine-containing compositions according to the invention have a shelf life of at least about 2 years when stored at temperatures between 5° C. and 25° C.

Example 5

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in a mixture of polyethylene glycol 400 and propylene glycol as indicated in Table 5 below. 5 mg/ml of lipoic acid was added as a stabilizing antioxidant. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed

As shown in Table 5, bendamustine, when dissolved in certain mixtures of polyethylene glycol and propylene glycol and a stabilizing amount of lipoic acid, had substantially no increase in total degradants after a period of 1 month. The data presented in Table 5 translates to bendamustine-containing compositions having a shelf life of at least about 2 years when stored at temperatures between 5° C. and at 25° C.

Example 6

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol and α -lipoic acid was added as a stabilizing antioxidant as indicated in Table 6 below. The samples were maintained at 40° C., 25° C. and 5° C. and analyzed for drug content and impurity profile as indicated in Table 6 below. The results obtained are presented in Table 6.

US 12,138,248 B2

11

12

TABLE 6

Stability of Bendamustine in 90% PEG 400, 10% PG and α -lipoic acid													
Formu- lation	Temp	Time Per.	Amt. mg/ml	% of Initial	% Area of degradants								% Total Imp.
BDM- 50 mg/mL α -lipoic acid- 10 mg/mL PEG 400:PG (90:10) qs to 1 mL	40° C.	Initial	51.0	100	0.20	0.06	<LD	<LD	<LD	<LD	<LD	LD	0.26
		1 M	50.5	99.0	0.21	0.31	0.13	0.07	0.13	0.10	<LD	<LD	0.95
		2 M	49.7	97.5	0.22	0.71	0.28	0.14	0.12	0.21	0.12	<LD	2.02
		3 M	48.7	95.5	0.22	1.01	0.45	0.21	0.14	0.37	0.16	0.05	2.96
	25° C.	3 M	50.5	99.0	0.20	0.36	0.07	<LD	<LD	0.10	<LD	<LD	0.73
		6 M	50.4	98.8	0.22	0.60	0.17	0.06	0.06	0.09	0.10	0.08	1.44
	5° C.	6 M	50.9	99.8	0.16	0.05	<LD	<LD	<LD	<LD	<LD	<LD	0.21
		12 M	50.6	99.2	0.20	0.18	<LD	<LD	<LD	<LD	<LD	<LD	0.38
		Initial	50.3	100	0.18	<LD	<LD	<LD	<LD	<LD	<LD	<LD	0.18
BDM- 50 mg/mL α -lipoic acid- 15 mg/mL PEG 400:PG (90:10) qs to 1 mL	40° C.	1 M	50.0	99.4	0.19	0.32	0.08	0.06	0.08	0.06	0.06	<LD	0.85
		2 M	49.8	99.0	0.19	0.65	0.21	0.12	0.13	0.23	0.14	0.06	1.85
		3 M	49.5	98.4	0.15	0.89	0.37	0.17	0.13	0.32	0.10	<LD	2.40
		6 M	47.0	93.4	0.20	1.76	0.66	0.19	0.31	0.47	0.33	0.17	4.93
	25° C.	3 M	50.0	99.4	0.20	0.35	0.08	<LD	<LD	<LD	0.11	<LD	0.79
		6 M	49.5	98.4	0.19	0.58	0.15	0.06	0.07	0.09	0.08	0.10	1.38
	5° C.	6 M	50.3	100	0.17	0.06	<LD	<LD	<LD	<LD	<LD	<LD	0.23
		12 M	50.2	99.8	0.19	0.15	<LD	<LD	<LD	<LD	<LD	<LD	0.34

<LD = Below Level of Detection

The data reported in Table 6 along with the data in Table 5 demonstrates that bendamustine solutions are stable when dissolved in mixtures of PEG and PG and 5-15 mg/mL α -lipoic acid. As shown in Table 6, bendamustine, when dissolved in combinations of polyethylene glycol and propylene glycol, in the presence of a stabilizing amount of lipoic acid, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6-12 months at 5° C. and 25° C. The data corresponds to bendamustine solutions being stable under ambient or refrigerated storage conditions for well in excess of 2 years, and thus long term stable.

Example 7

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 90% polyethylene glycol 400 and 10% propylene glycol. 2.5 mg/ml of thioglycerol was added as an antioxidant agent. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 7 below. The results obtained are presented in Table 7.

TABLE 7

Stability of Bendamustine in 90% PEG 400, 10% PG and Thioglycerol														
Formu- lation	Temp	Time Per.	Amt mg/ml	% of Initial	RRTs of degradants									% Total Imp.
BDM - 50 mg/mL Thio glycerol- 2.5 mg/mL PEG 400:PG (90:10) qs to 1 mL	40° C.	Initial	50.3	100	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	0.00
		15 d	50.2	99.8	BDL	BDL	0.18	BDL	BDL	BDL	0.05	0.08	BDL	0.31
		1 M	49.9	99.2	BDL	0.12	0.32	0.07	BDL	BDL	0.09	0.08	BDL	0.75
	25° C.	2 M	49.1	97.6	BDL	0.18	0.56	0.24	0.09	0.17	0.19	0.12	0.11	1.76
		3 M	48.8	97.0	BDL	0.23	0.85	0.34	0.16	0.30	0.34	0.29	0.19	2.94
		3 M	49.9	99.2	0.06	0.12	0.23	0.07	BDL	0.06	0.07	0.06	BDL	0.67
		6 M	49.3	98.0	BDL	0.23	0.53	0.22	0.11	BDL	0.21	0.22	0.20	2.07

BDL = Below Detectable Limit

The stability is similar to that of α -lipoic acid samples in Example 6 above. As shown in Table 7, bendamustine, when dissolved in a combination of polyethylene glycol and propylene glycol, and a stabilizing amount of thioglycerol, had less than 3% increase in total degradants after a period of 3 months at 40° C. Additionally, the same compounds had substantially no increase in total degradants after a period of 6 months at 25° C. The data reported supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for about 2 years.

Example 8

Bendamustine-containing compositions were prepared by dissolving bendamustine HCl to a concentration of 50 mg/ml in 85% PEG 400 and 15% PG in the presence of 5 mg/ml of thioglycerol. The samples were maintained at 40° C. and 25° C. and analyzed for drug content and impurity profile as indicated in Table 8 below. The results obtained are presented in Table 8.

US 12,138,248 B2

13

TABLE 8

Stability of Bendamustine in 85% PEG 400, 15% PG and Thioglycerol				
Formulation	Temp.	Time Period	Content (mg/mL)	% Total Imp.
BDM - 50 mg/mL		Initial	51.5	100
Thioglycerol - 5 mg/mL	40° C.	1 M	50.4	97.9
PEG 400:PG (85:15)	25° C.	1 M	51.4	99.8
qs to 1 mL		3 M	50.4	97.9
	5° C.	3 M	51.0	99.0

The stability is similar to that of thioglycerol samples in Example 7 above. As reported in Table 8, total impurities did not exceed 2% at 40° C. or 25° C. storage over one month, or at 25° C. and 5° C. storage after three months. The data reported in Table 8 supports the conclusion that these bendamustine solutions are stable under ambient or refrigerated storage conditions for at least about 2 years if not longer.

We claim:

1. A sterile container containing a liquid bendamustine-containing composition comprising bendamustine, or a pharmaceutically acceptable salt thereof, wherein the bendamustine concentration in the composition is about 25 mg/mL; a pharmaceutically acceptable fluid consisting of polyethylene glycol and optionally one or more of propylene glycol, ethanol, benzyl alcohol and glycofurol; and a stabilizing amount of an antioxidant, wherein the total impurities resulting from the degradation of the bendamustine is less than about 5% peak area response, as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of about 5° C. to about 25° C.
2. The sterile container of claim 1, wherein the antioxidant is monothioglycerol.
3. The sterile container of claim 1, wherein the antioxidant is monothioglycerol in a concentration of about 5 mg/mL.
4. The sterile container of claim 1, wherein the composition is stable for at least about 15 months at 5° C. or for at least about 15 months at 25° C.
5. The sterile container of claim 1, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and one or more of propylene glycol, ethanol, benzyl alcohol, and glycofurol.
6. The sterile container of claim 1, wherein the liquid bendamustine-containing composition comprises about 100 mg of bendamustine, or a pharmaceutically acceptable salt thereof.
7. The sterile container of claim 1, wherein the liquid bendamustine-containing composition comprises about 100

14

8. A liquid bendamustine-containing composition comprising

bendamustine, or a pharmaceutically acceptable salt thereof, and a stabilizing amount of an antioxidant, in a pharmaceutically acceptable fluid;

wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and optionally one or more of propylene glycol, ethanol, benzyl alcohol and glycofurol; and

wherein the bendamustine concentration in the pharmaceutically acceptable fluid is about 25 mg/mL,

wherein the total impurities resulting from the degradation of the bendamustine is less than about 5% peak area response, as determined by HPLC at a wavelength of 223 nm after at least about 15 months at a temperature of about 5° C. to about 25° C.

9. The composition of claim 8, wherein the antioxidant is monothioglycerol.

10. The composition of claim 8, wherein the antioxidant is monothioglycerol in a concentration of about 5 mg/mL.

11. The composition of claim 8, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and one or more of propylene glycol, ethanol, benzyl alcohol, and glycofurol.

12. The composition of claim 8, wherein the bendamustine concentration in the composition is 25 mg/mL.

13. The sterile container of claim 5, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol.

14. The sterile container of claim 5, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and propylene glycol.

15. The sterile container of claim 5, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and ethanol.

16. The sterile container of claim 5, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and benzyl alcohol.

17. The sterile container of claim 5, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and glycofurol.

18. The composition of claim 11, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol.

19. The composition of claim 11, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and propylene glycol.

20. The composition of claim 11, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and ethanol.

21. The composition of claim 11, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and benzyl alcohol.

22. The composition of claim 11, wherein the pharmaceutically acceptable fluid consists of polyethylene glycol and glycofurol.

* * * * *